tious and neoplastic processes. Unfortunately, neither CT nor MR is sufficiently specific for the precise diagnosis of the various possible brain lesions in AIDS. Because early appropriate therapy is of paramount importance in the immunosuppressed, our description of a CNS mass lesion due to *C immitis* emphasizes the importance of doing a biopsy of an accessible brain lesion in a patient with AIDS.

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Congestive Heart Failure and Sudden Death in a Young Woman With Thyrotoxicosis

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THE EXISTENCE OF "hyperthyroid heart disease" with resultant congestive heart failure has been a matter of controversy for a number of years. Some clinicians feel that thyrotoxicosis merely overstresses a heart with valvular, coronary, or other preexisting organic disease.[1] Other clinicians have reported congestive heart failure in patients in whom a careful search failed to reveal any other cause of heart disease and that resolved when the patients' thyrotoxicosis was treated.[1-11] Few postmortem evaluations of hearts of patients with presumed thyrotoxic congestive heart failure have been done to definitively confirm the absence of other significant disease. The death of this young thyrotoxic patient, who had congestive heart failure in the absence of atrial fibrillation, provided an opportunity to do anatomic, histologic, and biochemical evaluations of human myocardial tissue in this syndrome.

Methods

Clinical Testing

Thyroid function tests during the patient's early course were done at Consolidated Medical Laboratories, Highland Park, Illinois. Clinical tests during her final month were done at Michael Reese Hospital and Medical Center, Chicago. Thyroid-stimulating hormone (TSH) levels were determined using the Gammadab Kit (Travenol-Genetec Diagnostics, Cambridge, Mass).

Electron Microscopy of Myocardial Tissue

Myocardial tissue was taken at autopsy about 19 hours after death. Tissue for electron microscopy was fixed in 2.5% glutaraldehyde, postfixed in osmium tetroxide, dehydrated in graded alcohols, and embedded in epon. Sections were stained with uranyl acetate and lead citrate and were examined in a Philips 300 electron microscope.

Biochemical Characterization of Cardiac Myosin

Ventricular myosin was prepared as described by Offer and co-workers[12] with slight modifications used by Lompre and associates.[13] Myosin was prepared from this patient and from three human hearts from patients without thyrotoxicosis to serve as controls. The control patients had no history of heart disease, were not taking cardiac drugs, and their hearts had no evidence of significant disease. Myosin isotype composition was evaluated by a solution phase radioimmunoassay analysis using a monoclonal antibody to V3 cardiac myosin, as previously described.[14] Purified rat V1 and V3 isomyosins served as control standards. Rat V3 isomyosin was iodinated with sodium iodide I 125 by the lactoperoxidase procedure, and each myosin was evaluated for its ability to compete for antibody binding relative to the labeled rat V3. Logit transforms of combined data from two to four competition curves of each specimen were evaluated by linear regression analysis.

Results

Report of a Case

This 34-year-old woman had been generally well until January 1984, when she began having tremulousness, ner-

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ABBREVIATIONS USED IN TEXT

AV = atrioventricular
SSKI = saturated solution of potassium iodide
T_3 = triiodothyronine
T_4 = thyroxine
TSH = thyroid-stimulating hormone

vousness, heat intolerance, and diffuse headache. There was no history of heart disease. A small goiter was noted, but there was no ophthalmopathy, and hyperthyroidism was diagnosed. Treatment was begun with propylthiouracil, 50 mg given three times a day, and she felt better, but in March 1985, icterus, nausea, vomiting, and weight loss developed, and she had as many as eight bowel movements per day. Gallstones were not detected, and a liver biopsy specimen showed minimal nonspecific changes without eosinophils. The thyroid uptake of radioiodine was 59% at 24 hours, and 8 mCi of sodium iodide I 131 was administered. Giving methimazole worsened a rash present on the legs, so metoprolol tartrate and propylthiouracil, 50 mg three times a day, were prescribed.

Three months later she complained of heat intolerance and tremulousness. The thyroxine (T_4) level was 4.8 μg per dl, triiodothyronine (T_3) resin uptake 26%, and a T_3 level by radioimmunoassay was 590 ng per dl. Because the liver function test results had recently been abnormal, the propylthiouracil therapy was discontinued. During the next few weeks her tremulousness and nervousness worsened. In December 1985, a thyroid scan disclosed diffuse bilateral enlargement. The thyroid uptake of radioiodine was 55% at 6 hours and 34% at 24 hours. A dose of 28 mCi of ^{131}I was administered, and a week later a saturated solution of potassium iodide (SSKI), eight drops per day, was prescribed.

Two months later the patient had tachycardia and was tremulous. The T_4 level was 19.2 μg per dl, the T_3 resin uptake 40%, and the T_3 level by radioimmunoassay exceeded the upper limit of the test range of 800 ng per dl. The regimen of SSKI and metoprolol was continued, but she remained clinically and biochemically thyrotoxic.

The patient was then seen at the Michael Reese Endocrinology Clinic for evaluation. She complained of nervousness, tremulousness, and palpitations and had discontinued taking the SSKI and metoprolol a few days before coming to the clinic. She was thin, weighing 45 kg (100 lb), her blood pressure was 140/80 mm of mercury, and pulse 120 per minute and regular. There was no ophthalmopathy. The extraocular muscle movements were intact, as were the visual fields. The thyroid was firm and diffusely enlarged, with the right lobe measuring 7 by 4.5 cm and the left lobe 5.5 by 4 cm. The chest was clear, and the cardiac and abdominal examinations elicited no abnormalities. A pronounced tremor of the hands was present. The possibility of a TSH-producing pituitary adenoma was considered. Therapy with propranolol hydrochloride, 20 mg three times a day, was prescribed. A random TSH value was 1.5 μU per ml, which was barely detectable in the assay.

Two weeks later the patient felt generally improved. The tremulousness and palpitations had resolved, but she complained of nervousness, abdominal cramps, nausea, and right upper quadrant pain. Her pulse was 76 per minute and regular. She had minimal hand tremor. A coned-down x-ray film of the sella turcica was normal. A thyrotropin-releasing hormone test was done to detect a possible inappropriate elevation of TSH. The TSH levels at 0, 15, 20, and 30 minutes were 1.2, 0.9, 1.1, and 1.0 μU per ml, respectively. The T_4 value was 28 μg per dl, the T_3 resin uptake 52%, and a T_3 level by radioimmunoassay 671 ng per dl. It was concluded that the patient had Graves' disease rather than a TSH-producing tumor. Therapy with propranolol, 20 mg three times a day, was continued, and arrangements were made to admit the patient to an isolation room so that a large dose of ^{131}I could be administered.

Two weeks later the patient was admitted for pretherapy evaluation. She had no complaints of tremulousness or palpitations, but had chronic, dull, right upper quadrant pain. She was afebrile, her blood pressure was 140/80 mm of mercury, pulse rate was 80 per minute and regular, and respirations were 20 per minute. On examination, the head and thyroid were unchanged. Examination of the chest disclosed dullness at the right base to percussion and auscultation without rales. On cardiac examination, the point of maximal impulse was dynamic and was displaced laterally 2 cm in the fifth intercostal space. There was a grade II/VI holosystolic murmur at the apex radiating to the axilla and a murmur at the left lower sternal border that was unchanged with respirations. The jugular venous pulse had prominent ventricular waves and was elevated 10 cm. The abdomen was flat, soft, and nontender, with normal bowel sounds. There was trace pedal edema.

The hematocrit was 35%, leukocyte count was 6,000 per μl with a normal differential, and the platelet count was normal. The serum sodium, chloride, bicarbonate, urea nitrogen, creatinine, and creatine kinase levels were normal. The serum potassium value was 3.5 mEq per liter. The total bilirubin level was 1.2 mg per dl, and alkaline phosphatase 337 normalized units per dl (normal 25 to 100). The serum aspartate and alanine aminotransferase levels were normal. The urine was yellow, cloudy, and had a specific gravity of 1.012, a pH of 5, 1+ protein, 4+ occult blood, 4 erythrocytes per high power field, and a few squamous cells. Moderate cardiomegaly was present on a chest x-ray film. There was a right pleural effusion and a small left pleural effusion. The lung fields were clear, and the pulmonary vasculature was normal. The electrocardiogram showed a sinus rhythm, a rate of 69, accelerated atrioventricular (AV) conduction, and repolarization changes consistent with left ventricular hypertrophy.

Combined M-mode and two-dimensional echocardiographic studies showed the left atrium to be moderately dilated to 3.8 cm, 2.7 cm per m^2 (normal < 2.2 cm per m^2). The left ventricular chamber was also slightly increased in size. The right ventricular and right atrial chambers were severely dilated, and there was paradoxic septal wall motion. The overall left ventricular contraction was diffusely hypokinetic. All valves appeared to be normal. A pattern consistent with pulmonary hypertension with loss of the a wave was noted, however. A Doppler study detected mild mitral regurgitation, severe tricuspid regurgitation, and pulmonic regurgitation consistent with pulmonary hypertension. A bubble study showed persistence of bubbles compatible with tricuspid regurgitation. There was no evidence of an atrial septal defect or a right-to-left shunt. The mitral valve excursion was 14 mm and intraventricular septal thickness 9 mm. The posterior wall thickness was 8 mm and excursion 10 mm. The left

ventricular chamber diameter was 5.3 cm in diastole and 4.3 cm in systole.

In view of her somewhat low serum potassium level, a single oral dose of 40 mEq of potassium chloride was administered in anticipation of diuretic therapy. She was in a private room for the anticipated ^{131}I therapy, and a few minutes after the potassium was administered, she was discovered to be in full cardiac arrest and was not successfully resuscitated.

Necropsy Findings

The thyroid was enlarged, weighing 73.7 grams. Sections showed a largely involuted, diffuse hyperplasia (Figure 1) and no evidence of thyroiditis. Her thymus was large for her age, weighing 47.2 grams. Other than a few B-lymphocyte aggregates, without germinal center formation, it showed a normal architecture. The heart weighed 295 grams and showed dilatation of all chambers, more prominent on the right. There was pronounced left ventricular endocardial fibroelastosis. No valvular lesion or evidence of coronary artery disease was seen. Light microscopy revealed varying myocardial cell size, hyperlobated nuclei, focal severe interstitial fibrosis, and scattered round cell infiltrates (Figure 2). On electron microscopy there was a mild increase in variably sized mitochondria (Figure 3). There were also scattered electron-dense granules seen within mitochondria. Cristal architecture could not be assessed accurately due to postmortem autolysis.

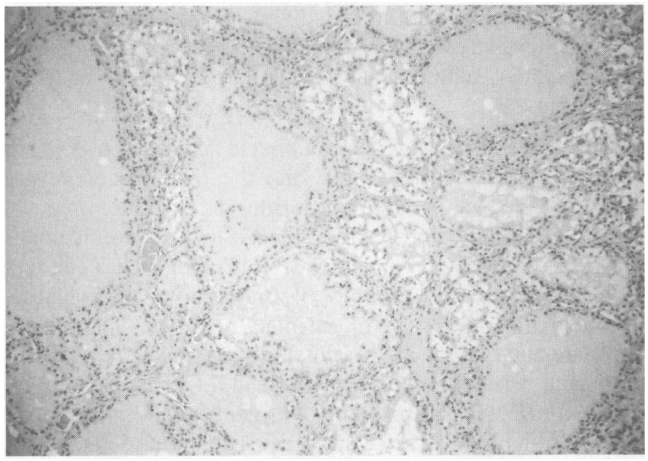

Figure 1.—The photomicrograph shows the histologic appearance of the thyroid. There was a generally involuted, diffuse hyperplasia and no evidence of thyroiditis (hematoxylin and eosin, original magnification × 110).

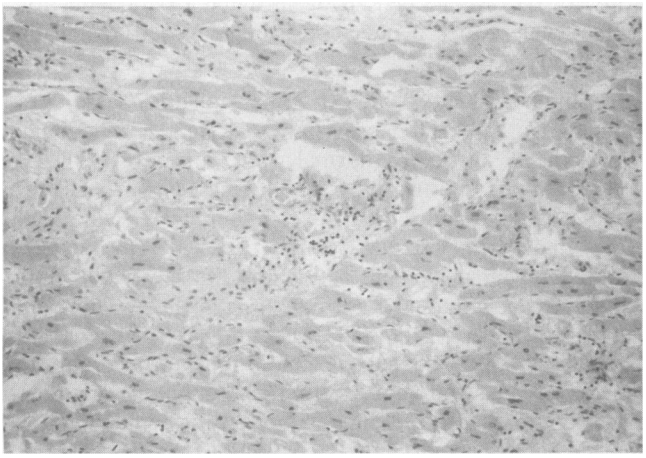

Figure 2.—The photomicrograph shows the histologic appearance of the heart. Myocardial cells varied in size and had hyperlobated nuclei. There were focal severe interstitial fibrosis and scattered round cell infiltrates (hematoxylin and eosin, original magnification × 140).

Biochemical Characterization of Cardiac Myosin

Myosin was prepared from myocardial tissue from this patient and from three human hearts from nonthyrotoxic patients to determine whether the proportions of V1 and V3 myosin isotypes were altered by thyrotoxicosis. Myosin isotype composition was evaluated by radioimmunoassay using a monoclonal antibody to V3 cardiac myosin. The results (Figure 4) do not indicate any detectable difference in myosin isotypes in the thyrotoxic patient compared with the controls.

Discussion

Cardiac function has long been known to be altered in patients with thyrotoxicosis. In 1825 Parry described the cases of eight patients with exophthalmos and goiters who also had palpitations, irregularity of the pulse, edema, and cardiac enlargement.[15] Some clinicians maintained that thyrotoxicosis alone could cause heart disease,[1-11] while others thought that associated heart disease, such as coronary artery disease, was always present in such patients in addition to thyrotoxicosis.[1] This question was addressed by Sandler and Wilson in 1959.[1] Of their 462 patients with thyrotoxicosis, 150 had evidence of cardiac dysfunction—auricular fibrilla-

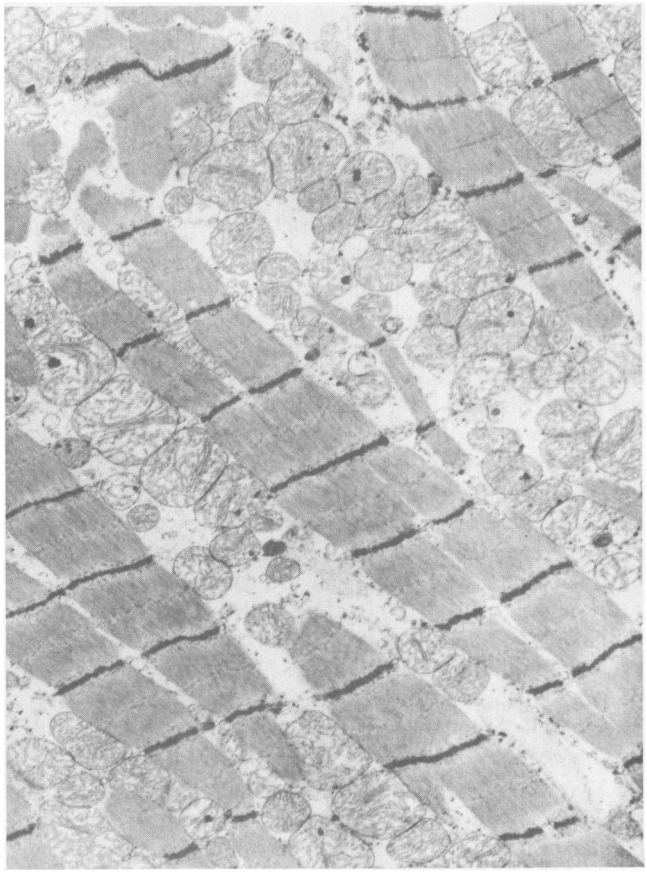

Figure 3.—On electron microscopy of the myocardium, the mitochondria were mildly increased in number, and some contained electron-dense granules (original magnification × 15,732).

tion, congestive heart failure, cardiomegaly, or all three. Of these 150 patients, 64 (43%) had no clinical, radiologic, or electrocardiographic evidence of any associated heart disease. Neither the duration nor the severity of thyrotoxicosis appeared to be relevant factors in producing cardiac complications in these 64 patients. Of particular relevance to the present case, of the 26 patients with congestive heart failure in this group, 23 also had auricular fibrillation that was thought to be a significant contributing factor. Thus, our case was similar to only three described by these workers in which the patients had sinus rhythm, congestive heart failure, but no evidence of associated cardiac disease. More recently there have been several reports of a reversible cardiomyopathy in thyrotoxicosis,[8,9] especially in children.[11] The untimely death of our patient provided a unique opportunity to anatomically document the absence of unsuspected organic heart disease in a patient with presumed "thyrotoxic heart disease" and to do histologic and biochemical analyses of the myocardial tissue.

Tachycardia and a bounding precordium are typical clinical signs in cases of thyrotoxicosis. In addition to its increased rate, the heart manifests an increased stroke volume, cardiac output, and pulse pressure, and the circulation time is decreased.[16] Cardiac blood flow and myocardial oxygen consumption are increased, and the velocity of contraction is shortened.[17] Experimentally induced thyrotoxicosis in animals causes a change in the pattern of myosin isoenzymes, but this has not been reported in humans.[18-26] Thyroxine greatly increases the number of mitochondria in heart muscle cells.[27,28] Myocardial hypertrophy has been described both in animals given thyroid hormones[23,29-31] and in humans with hyperthyroidism.[32,33]

Formerly it was thought that thyroid hormones mediated these effects on the myocardium by the action of catecholamines on the adenylate cyclase system. Levey and Epstein

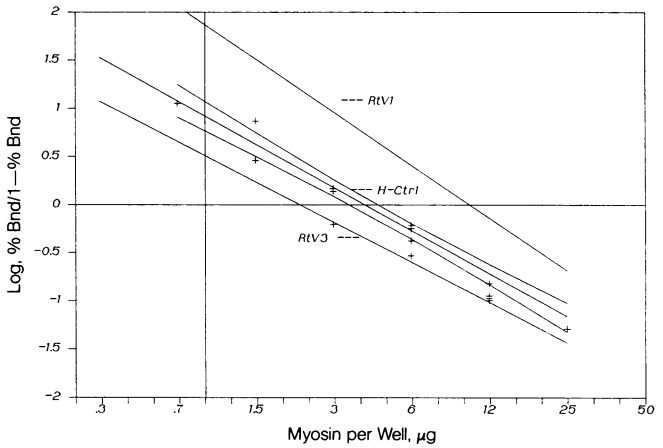

Figure 4.—The graph shows the results of radioimmunoassay analysis of human thyrotoxic myosin. Increasing amounts of standard rat V1 myosin **(top line),** myosin prepared from control human myocardium **(center line),** and of standard rat V3 myosin **(lowest line)** were used to compete for binding of rat V3 labeled with iodine 125 with a monoclonal antibody to rat V3. For clarity, data points for the three regression lines have been omitted, and curves representing the 95% confidence limits are shown for the control human myosin only; the confidence limits for the other lines were comparable. The data points (+) for incubations using myosin prepared from the thyrotoxic patient's myocardium are plotted. There was no difference in the competitive binding of thyrotoxic myosin to monoclonal V3 antibody compared with control human myosin.

proposed, however, that there are separate adenylate cyclase systems for thyroid hormones and catecholamines,[34] and this topic has been addressed in a recent review.[35] It is now accepted that in hyperthyroidism myocardial tissue has a normal sensitivity to catecholamines, and plasma catecholamine levels are not increased. In isolated cat papillary muscle, the level of thyroid hormone greatly affects the intrinsic contractile state, independent of noradrenaline stores and alterations in high-energy phosphates. Thyroid hormones may also alter the intracellular handling of calcium by myocardial cells.[33]

Although thyroid hormones generally have positive inotropic and chronotropic effects, unexplained congestive heart failure without dysrhythmia has occasionally been reported, as noted above. Several studies have indicated that mild pulmonary hypertension exists in thyrotoxic patients.[36,37] Bishop and colleagues found that the work of the right ventricle was increased, in part due to the increased blood volume and more rapid venous return.[37] Tricuspid regurgitation is often seen in severe right ventricular failure and is believed to be due to right ventricular dilatation rather than to primary valvular disease. Dougherty and Craige reported two cases of apathetic hyperthyroidism in elderly patients that presented as tricuspid regurgitation and severe congestive heart failure.[5] Characteristic jugular venous pulse tracings with exaggerated C and V waves and steep y descent were documented. Both patients responded dramatically to treatment of their thyrotoxicosis. Associated organic heart disease was believed to be mild, but this was not proved histologically.

An autopsy examination in the present case disclosed that the heart was dilated with left ventricular endocardial fibroelastosis, which suggested a chronic congestive cardiomyopathy. The fibroelastosis was extensive and may have compromised ventricular function in this patient; it is not clear whether the fibroelastosis represented an independent pathologic process or was related to the hyperthyroidism. There was no evidence that the compromised cardiac function resulted from ischemic, hypertensive, valvular, or congenital heart disease. Our patient did not abuse drugs or alcohol, and there was no evidence to suggest cardiomyopathy due to viral infection, amyloidosis, hemochromatosis, sarcoidosis, connective tissue disease, neuromuscular disease, neoplasia, glycogen storage disease, or lipoidosis.

Previous reports of myocardial histologic findings in hyperthyroidism were summarized by Saphir[38] and included nonspecific findings, such as histiocytic, lymphocytic, and fibroblastic cellular accumulations; edema and necrosis; swollen fibers with indistinct striations and lipoid changes; hyalin replacement of muscle fibers; myocardial hypertrophy; and, in some cases, no changes. Ultrastructurally, increased numbers, size, and complexity of mitochondria have been reported in animals after thyroxine administration[27,39]; our observation of dense granules associated with cristae is of uncertain significance and may represent a postmortem change. The findings in our case of a focal interstitial fibrosis with a mild round cell infiltrate and increased numbers of mitochondria, although nonspecific, are consistent with some of these observations.

A biochemical analysis of myosin isotypes present in human myocardial tissue from a patient with thyrotoxicosis has not previously been published. In rats and rabbits, administering thyroid hormone in high doses causes the V1

isoform to increase relative to the V3 isoform.[18-26] Several methods have been devised for estimating cardiac myosin isoforms: adenosine triphosphatase-specific enzyme activity of purified myosin; mobility of native myosin isoforms on pyrophosphate, nondenaturing gels; and immunologic analysis. Comparison of these methods by others has shown that none could give a totally reliable estimate of the exact isomyosin composition in humans. Mercadier and co-workers reported that normal fetal and adult human myocardium contains both V1 and V3 isoforms but that the predominant isoform is of the V3 type,[25] as was also shown by Clark and associates.[14] Mercadier found that the maximum proportion of V1 expressed in the normal population was about 15%. Their study used an affinity purified polyclonal anti-V1 antibody rather than monoclonal anti-V3 as used in our study. Although use of an anti-V1 probe provides greater sensitivity for detecting the V1 isotype, the V3 antibody used here would have been able to detect the expression of the V1 isotype had it exceeded 25%. This level of V1 expression was not observed in the thyrotoxic tissue. This result is not an artifact of autolysis during the 19-hour period after the patient's death because intact myosin was extracted from the tissue, and the monoclonal antibody used will recognize denatured and trypsinized V3 isomyosin.

In view of the autopsy findings, our patient is thought to have died of a sudden ventricular arrhythmia. Although atrial fibrillation may occur in about 20% of patients with thyrotoxicosis, other cardiac arrhythmias are uncommon, and sudden death has rarely been reported. Atrial fibrillation was found in 207 of 1,000 cases of thyrotoxicosis reported by Ernstene[40] and in 84 of 462 cases reported by Sandler and Wilson.[1] Less common dysrhythmias and conduction disturbances[41,42] were atrial flutter, first- and second-degree AV block, third-degree AV block, reversible bundle branch block, ventricular ectopic beats, ventricular tachycardia, and ventricular fibrillation.

In 1923 Bickel described two cases of sudden death in patients with hyperthyroidism that he attributed to ventricular fibrillation.[43] In 1945 Boone described the case of a 37-year-old woman with hyperthyroidism who had electrocardiographic proof of a period of ventricular fibrillation; because she recovered, no anatomic proof of the absence of other heart disease was obtained.[44] Lyngborg and Jacobsen reported the case of a 59-year-old man with thyrotoxicosis who died of intractable ventricular tachycardia,[45] and they comment that theirs is the first such case of thyroid hormone-induced fatal ventricular tachycardia to have been reported. Of note, their patient had mild diabetes mellitus and hypertension and was admitted to hospital following a posterior wall myocardial infarction two weeks before his death, so coronary artery disease and acute myocardial ischemia likely played important roles in the genesis of his arrhythmia. Parker and Lawson published a series of 33 patients who died primarily of thyrotoxicosis.[46] Factors that indicated a poor prognosis included tachycardia (greater than 120 beats per minute), atrial fibrillation, congestive heart failure, and thyroid crisis. Of these patients, 18% had a major embolism and 61% (20 patients) had congestive heart failure. Five patients (15%), however, died suddenly and unexpectedly, and necropsy showed no evidence of a myocardial infarction or pulmonary embolus. Thus, the sudden death of our young patient must be viewed as an extremely unusual event.

In conclusion, we were unable to document other organic heart disease in a young patient with cardiomyopathy thought to be due to thyrotoxicosis. Despite the poor myocardial function clinically, a normal V3 isotype of myosin predominated in this patient, unlike the situation in some thyrotoxic animal model systems in which the V1 isotype increases. Factors other than an altered myosin isotype may contribute to poor myocardial function in some humans with thyrotoxicosis.

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Irreversible Interstitial Pneumonitis Associated With Tocainide Therapy

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THE ADMINISTRATION OF several chemotherapeutic, antibiotic, and antiarrhythmic agents has been associated with the development of an interstitial pneumonitis indistinguishable histologically from the idiopathic form.[1,2] Previous case reports have described an alveolitis caused by tocainide therapy.[3,5] In each case, the pulmonary changes were responsive to cessation of the drug therapy and administering corticosteroids. We report a case of an acute interstitial pneumonitis developing in a patient receiving tocainide that was rapidly and irreversibly progressive, resulting in death despite discontinuing the use of the drug and promptly initiating steroid therapy.

Report of a Case

The patient, an 80-year-old man, had myocardial infarction complicated by congestive heart failure in October 1985. After the infarction his resting left ventricular ejection fraction was determined to be 21% by gated wall motion radionuclide study. Before discharge, a chest x-ray film showed cardiomegaly and findings consistent with mild residual congestive heart failure without evidence of intrinsic pulmonary disease (Figure 1). In February 1986, he presented to our hospital because of increasing shortness of breath and cough for three days before admission. He said he did not have associated coryza or hemoptysis. On admission he had a blood pressure of 108/80 mm of mercury, a heart rate of 90 beats per minute, respirations of 24 to 28, and a temperature of 38.7°C (101.6°F). Examination of the lungs revealed bilateral rales. His chest x-ray film showed extensive bilateral interstitial infiltrates (Figure 2). Blood gas determinations made with the patient breathing room air showed a pH of 7.54, partial oxygen pressure of 63 torr, oxygen saturation 94%, and partial pressure of carbon dioxide 32 torr. His medication regimen at admission was the following: nifedipine (Procardia), 10 mg three times a day; furosemide (Lasix), 40 mg a day; digoxin, 0.25 mg a day; nitroglycerin (Transderm-Nitro); captopril, 25 mg three times a day; and tocainide, 400 mg three times a day. Tocainide therapy had been started for recurrent nonsustained ventricular tachycardia three months before he was admitted.

During the patient's hospital admission, administration

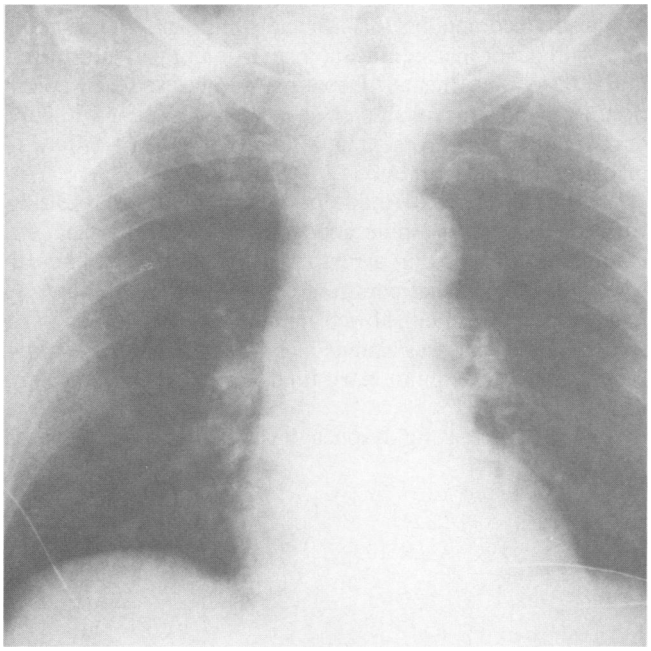

Figure 1.—The October 1985 chest x-ray film shows cardiomegaly without evidence of intrinsic pulmonary disease.

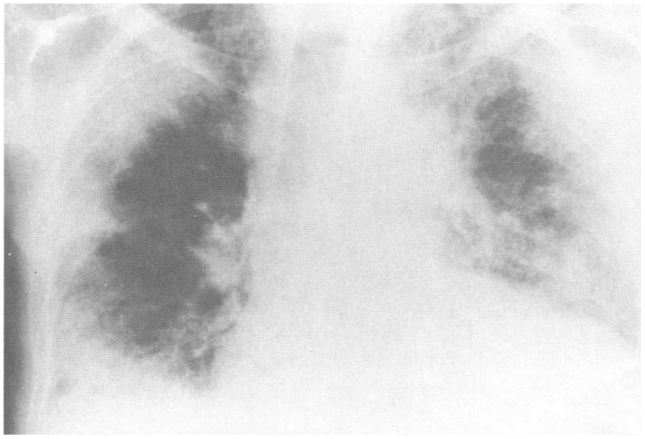

Figure 2.—A chest x-ray film on admission shows extensive interstitial infiltrates with relative sparing of the perihilar region.

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